Cannabinoids for treating neurogenic lower urinary tract dysfunction in patients with multiple sclerosis: a systematic review and meta-analysis

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Abstract: OBJECTIVES To systematically review all available evidence on efficacy and safety of cannabinoids for treating neurogenic lower urinary tract dysfunction (NLUTD) in patients with multiple sclerosis (MS). PATIENTS AND METHODS The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were identified by electronic search of Cochrane register, Embase, Medline, Scopus (last search on 11 November 2016). RESULTS After screening 8469 articles, two randomized controlled trials and one open label study enrolling a total of 426 patients, were included. Cannabinoids relevantly decreased incontinence episodes in all three studies. Pooling data showed mean difference in incontinence episodes per 24 hours to be -0.35 (95% confidence interval -0.46 to -0.24). Mild adverse events were frequent (38-100%), but only two patients (0.7%) reported a serious adverse event. CONCLUSIONS Preliminary data imply, that cannabinoids might be an effective and safe treatment option for NULTD in patients with MS. However, evidence base is poor and more high-quality, well-designed, adequately powered and sampled studies are urgently needed to reach definitive conclusions.

DOI: https://doi.org/10.1111/bju.13759

Originally published at:
Abo Youssef, Nadim; Schneider, Marc P; Mordasini, Livio; Ineichen, Benjamin V; Bachmann, Lucas M; Chartier-Kastler, Emmanuel; Panicker, Jalesh N; Kessler, Thomas M (2017). Cannabinoids for treating neurogenic lower urinary tract dysfunction in patients with multiple sclerosis: a systematic review and meta-analysis. BJU International, 119(4):515-521.
DOI: https://doi.org/10.1111/bju.13759

Received Date : 19-Jul-2016

Revised Date : 25-Nov-2016

Accepted Date : 22-Dec-2016

Article type : Cochrane Review

Cannabinoids for treating neurogenic lower urinary tract dysfunction in patients with multiple sclerosis: a systematic review and meta-analysis

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bju.13759

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Key words: neuro-urology, neurogenic lower urinary tract dysfunction (NLUTD), multiple sclerosis (MS), cannabinoids, systematic review, meta-analysis

Abstract

Objectives: To systematically review all available evidence on efficacy and safety of cannabinoids for treating neurogenic lower urinary tract dysfunction (NLUTD) in patients with multiple sclerosis (MS).

Patients and methods: The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were identified by electronic search of Cochrane register, Embase, Medline, Scopus (last search on 11 November 2016).

Results: After screening 8469 articles, two randomized controlled trials and one open label study enrolling a total of 426 patients, were included. Cannabinoids relevantly decreased incontinence episodes in all three studies. Pooling data showed mean difference in incontinence episodes per 24 hours to be -0.35 (95% confidence interval -0.46 to -0.24). Mild adverse events were frequent (38-100%), but only two patients (0.7%) reported a serious adverse event.

Conclusions: Preliminary data imply, that cannabinoids might be an effective and safe treatment option for NULTD in patients with MS. However, evidence base is poor and more high-quality, well-designed, adequately powered and sampled studies are urgently needed to reach definitive conclusions.

1. Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) is highly prevalent in patients with multiple sclerosis (MS) and substantially impairs quality of life (1, 2). The prevalence of NLUTD appears to be related to the duration of MS and is reported by almost all patients suffering from MS for more than 10 years (1, 3). Treatment of NLUTD in the MS population is a significant challenge, especially since standard therapies often fail. Thus, therapeutic alternatives are urgently needed.

Cannabinoids, a heterogenous group of endogenous molecules and others that are metabolites of phytocannabinoids (4), were reported to improve tremor and spasticity in animal models (5) and questionnaire-based reports suggested beneficial effects of recreational cannabis use in patients with MS suffering from NLUTD (6). Cannabinoids are presumed to reduce detrusor contractility via cannabinoid receptors (7, 8) expressed both in the detrusor and central nervous system (9). However, cannabinoid-mediated actions on lower urinary tract function are complex

and not yet fully understood. Considering the potential of cannabinoids for medical use (10), we performed a systematic review to assess and appraise the evidence on efficacy and safety of cannabinoids in the treatment of NLUTD in patients with MS.

2. Evidence acquisition

2.1 Data sources and searches

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (11). A review protocol was elaborated, which is available on PROSPERO (CRD42014010142) (http://www.crd.york.ac.uk/PROSPERO). We systematically searched Cochrane Central Register of Controlled Trials, Embase, Medline, and Scopus from 1 January 1946 to 11 November 2016. No language restriction was applied. We additionally searched the reference lists of all included studies and any relevant review articles. Moreover, we looked for (on 23 November 2016) unpublished (ongoing) research in ClinicalTrials.gov and the ISRCTN registry, but no additional studies have been identified. The search strategies are illustrated in Web supplement 1.

2.2 Study selection

We aimed to include all original studies that reported efficacy and/or safety data on cannabinoids for treating NLUTD in female and male patients with MS, including randomized controlled trials (RCTs), comparative non-RCTs, and single-arm cohort studies. Non-original articles, those including children only, and those not discriminating between patients with MS and other neurological/non-neurological disorders were excluded. All identified abstracts were imported into bibliography

management software (EndNote X7, Thomson Reuters, 1500 Spring Garden Street, Fourth Floor Philadelphia, PA 19130, USA) and filed according to inclusion and exclusion folders by drag and drop. Abstracts of all identified studies were independently reviewed by two authors (NAY, MPS and LM). Studies reporting on cannabinoids for treating NLUTD in patients with MS were reviewed in full text.

2.3 Data extraction and risk of bias assessment

The variables assessed included year of publication, type of study, type of cannabinoid, type of combination of cannabinoid, treatment duration, number of patients, gender and age, improvement of incontinence and nocturia episodes, number of daytime voids, adverse events and withdrawals. Data from eligible reports were extracted in duplicate (NAY and MPS) and discrepancies were resolved by a third reviewer (TMK).

The Cochrane Risk of Bias Assessment tool was used for RCTs (12). This included the assessment of sequence generation, allocation concealment, blinding of participants, therapists, and outcome assessors, completeness of outcome data, and selective outcome reporting (Web supplement 2). The risk of bias in the comparative non-RCT was assessed using the Cochrane tool and an extra item to estimate the risk of findings being explained by confounding (Web supplement 2). This is a pragmatic approach recommended by methodological literature to assess risks of bias in non-randomized studies (13-15). A list of the 5 most important confounders for efficacy and safety outcomes was developed with clinical content experts (members of the International Continence Society Neuro-Urology Promotion Committee). The confounding factors are gender, age, urinary tract infections, degree of disability (Expanded Disability Status Scale (EDSS) / duration of

neurological disease) and other medications. In addition, external validity was taken into account by assessing whether study participants were selected consecutively and whether the specified confounding factors were comparable between the treatment groups. Attrition bias and selective outcome reporting were also assessed (Web supplement 2). This is also a pragmatic approach informed by the methodological literature (12).

Finally, conflict of interest declaration, reporting of funding source and role of funding source was investigated.

2.4 Data synthesis

We constructed two-by-two tables for each of the included studies and calculated the effect size (ES) and corresponding 95% confidence intervals (CI). Since data were sparse, we performed only an exploratory analysis, ignoring differences in study design. The missing control group of the open label study was replaced by a norm-control group, generated by the mean values of the two control groups from the RCTs. We pooled the effect size using a random effects model. Forest plots were generated in order to provide a visual representation of results and to illustrate the direction and magnitude of effects. Analyses were performed using the *metan* command of the Stata statistics software package (Stata 14.0 and 9.0 statistics software package; StataCorp 2009. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Risk of bias summary and graph (Web supplement 2) was generated using Cochrane RevMan software (RevMan v 5.3; Informatics and Knowledge Management Department; Cochrane, St Albans House, 57-59 Haymarket, London, UK).

3. Evidence synthesis

3.1 Search results

The PRISMA flow diagram chart (Figure 1) illustrates the literature search and results. After screening of 8469 abstracts, 3 studies have been included in the qualitative and quantitative synthesis.

3.2 Study and patient characteristics (Table 1)

Two of the 3 included studies, were RCTs (16, 17) and one was an open label study (18). Overall, the 3 included studies enrolled a total of 426 patients: 289 women (68%), 122 men (29%), and 15 (3%) patients where the gender was not reported. The study by Brady et al. (18) was an open label study with a two phased follow up: initial combination therapy with 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) for eight weeks, followed by a single THC-only therapy for further eight weeks.

3.3 Efficacy of cannabinoids

Cannabinoids relevantly decreased incontinence episodes in all three studies (Table 2). Pooling data showed mean difference in incontinence episodes per 24 hours to be -0.35 (95% confidence interval -0.46 to -0.24) (Figure 2). In addition, a significant decrease of nocturia episodes, number of daytime voids and number of voids per 24 hours was found in one study (Table 2).

3.4 Safety of cannabinoids

The most common adverse events are illustrated in Table 1. The general number of mild adverse events was high (38-100%), but only two patients (0.7%, 2/277 patients) reported a serious adverse event (one haemorrhagic cystitis and one possible transient ischaemic attack, both with unclear causality).

3.5 Risk of bias and confounding

The risk of bias and confounding was high in the non-RCT (18) (Web supplement 2).

3.6 Conflict of interest, funding source and role of founding source

Conflict of interest was only disclosed by Kavia et al. (16). Non-company funding was reported by Brady et al. (18) and by Freeman et al. (17), whereas the study by Kavia et al. (16) was fully funded by the manufacturer company. None of the studies reported on the role of the founding source.

4. Discussion

4.1 Principal findings

Improvements in incontinence rates, nocturia, daytime and 24-hour voids, as well as a limited number of severe adverse events suggest that cannabinoids may be effective and safe for treating NLUTD in patients with MS. Although our findings are promising, the evidence was confined to 3 studies with a very limited overall number of treated patients in this systematic review.

4.2 Findings in the context of existing evidence

The endocannabinoid system is involved in regulation of LUT function, possibly at several levels of the micturition pathway (9). Studies in experimental animal models have demonstrated the role of the cannabinoid receptors in sensory signalling and afferent bladder functions, as well as a possible modulatory effect on cholinergic nerves (19). Fatty acid amide hydrolase (FAAH), which degrades endocannabinoids and fatty acid amides, is present both in the bladder mucosa and the central nervous system controlling lower urinary tract function. Inhibition of FAAH in rat models has been shown to be associated with a modulation of cannabinoid type 1 (CB1) and type 2 (CB2) receptors in the spinal cord. In addition, endogenous spinal cannabinoid receptor ligands seem to be involved in the regulation of normal micturition and detrusor overactivity (9, 20).

Cannabis is one of the most popular recreational drugs worldwide and it is speculated that 178 million people in the age group 15 to 64 years have used it at least once in the year 2012 (10). There are approximately 60 pharmacologically active compounds extracted from the marijuana plant and the most popular is THC with psychoactive effects that are related to the concentration in the applied preparation (21). Because of the delay in onset of effect and narrow therapeutic window with resultant predilection for adverse effects, THC is administered in combination with another phytocannabinoid, such as CBD (22). Over the years, there has been a growing interest in the medical use of cannabis in treating disease and alleviating symptoms. Summarizing RCTs to assess the benefits and adverse events of cannabinoids, indicates that there is moderate-quality evidence supporting prescription cannabinoids as an effective and safe treatment of chronic neuropathic or cancer pain, sleep disorders and spasticity due to MS (10, 23). However, a

statistical significance was not reached in any of the clinical trials. Nevertheless, cannabinoids are particular interesting because of the favourable safety profile as severe side effects are very rare.

4.3 Implications for research

Prescription cannabinoids are becoming a well-established pharmacological treatment for pain and other diseases with a favourable safety profile (10). The preliminary data summarized in this systematic review suggests potential benefits of cannabinoids for treating NLUTD in both female and male patients with MS and therefore further clinical trials are warranted. Appropriately designed multicentric RCTs are necessary to assess validated disease- and condition-specific quality of life data, urodynamic findings, short-, medium- and long-term outcomes, safety, as well as cost-effectiveness issues.

Despite many animal studies on cannabinoids and their function, the mechanism of action is not yet fully understood and in particular the effects of cannabinoids for treating NLUTD remain to be elucidated. Hence, further animal studies addressing the potential mechanism of action of cannabinoids for treating NLUTD are warranted.

4.4 Implications for practice

The progressive nature of the course of disease in MS influences NLUTD and thereby impacts the effect of therapy (1). Thus, cannabinoids might be successful at the beginning in a patient with MS but lose efficacy as the disease progresses. Nevertheless, cannabinoids open another therapeutic avenue for managing NLUTD in patients with MS. The safety profile is favourable and cannabinoids are devoid of the adverse effects associated with other more commonly used agents such as

blurred vision or constipation, which are particularly relevant in neurological patients. Moreover, this treatment is not associated with a risk for voiding dysfunction in contrast to most of the other therapeutic options and is particularly attractive to patients with MS where catheterisation and associated complications are a real concern. The general practitioner and/or neurologist may initiate the neuro-urological treatment considering that the risk of developing upper urinary tract damage and renal failure is much lower in patients with slowly progressive non-traumatic neurological disorders such as MS and Parkinson's disease than in those with spinal cord injury or spina bifida (1). The treatment goals of cannabinoids vary between different neurological disorders. Thus, dose- and disease-specific studies are warranted and continuous versus on demand medication has to be further assessed. In addition, cannabinoids might be considered as a treatment improving different quality of life issues of the patient with MS including NLUTD. Taking into account the potential of cannabinoids in medical use (10), it seems worth to try it out before more invasive treatments are established.

4.5 Limitations of this study

Although this report represents, to the best of our knowledge, the first study that systematically reviewed and synthesized all available evidence of cannabinoids for treating NLUTD in patients with MS, there are limitations that should be addressed. The number of included articles, the number of investigated patients and the follow-up was very limited. Moreover, the severity of MS and the NLUTD has not been reported. In addition, the missing control group of the open label study was replaced by a norm-control group generated by the mean values of the two control groups from the RCTs for statistical analysis. In the absence of robust evidence there is a

trade-off between the level of methodological rigor of an analysis and the efficiency. Using the base-rate of the two RCTs allowed us to incorporate the single-arm study. In view of the fact that any result derived from 2 or 3 studies will be exploratory, we decided to stick to this approach. Standard deviations for baseline and follow-up measurements were missing in most outcome measures and the between-study heterogeneity was substantial. More detailed methodological study limitations are described in Web supplement 3.

5. Conclusions

The currently available evidence implies that cannabinoids may be effective and safe for treating NLUTD in patients with MS. However, although we identified 2 RCTs, the reported outcomes, number of investigated patients and follow-up were very limited and the between-study heterogeneity was substantial. Thus, our systematic review, although suggesting that the treatment with cannabinoids seems to be a promising option for NLUTD in patients with MS, has shown the urgent need for well-designed, adequately sampled and powered RCTs to reach definitive conclusions.

Conflict of interest disclosures: Nadim Abo Youssef, Marc P. Schneider, Livio Mordasini, Benjamin V. Ineichen, Lucas M. Bachmann, Emmanuel Chartier-Kastler, Jalesh N. Panicker and Thomas M. Kessler have nothing to disclose.

Funding/Support: This study was supported by the Swiss Continence Foundation and a MD-PhD scholarship to MPS and BVI of the Swiss Academy of Medical Sciences (SAMS). JNP is supported in part by funding from the United Kingdom's Department of Health NIHR Biomedical Research Centres funding scheme.

Role of the sponsor: The Swiss Continence Foundation, the Swiss Academy of Medical Sciences (SAMS) and the United Kingdom's Department of Health NIHR Biomedical Research Centres had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgments: This work has been promoted by the International Continence Society (ICS) Neuro-Urology Promotion Committee (http://www.ics.org/committees/neurourology).

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Table 1. Characteristics of included studies

	Reference	Year of publication	Total number of patients (female/ male)	Type of intervention	Type of cannabinoid	Dose/day in mg	Application	Treatment duration in weeks	Mean age in years	Mean MS duration in years	Adverse events: number of patients	Most common type of adverse event, >5% of the patients (number of patients)	Withdrawal: cause (number of patients)	Outcomes measured
RCTs	Freeman et al. [17]	2006	81 (52/29)	Control	Placebo	Max. 25	Capsule	13	50.2	NR	73	UTI	NR	IE24, PT
			86 (62/24)	Experimental	THC	Max. 25	Capsule	13	49.9	NR	62	UTI	NR	IE24, PT
			88 (60/28)	Experimental	CBD	Max. 25	Capsule	13	50.6	NR	64	UTI	NR	IE24, PT
	Kavia et al. [16]	2010	68 (46/22)	Control	Placebo	Max. 129/120	Spray	8	47	NR	18 (2 SAE)	Dizziness (4), UTI (4)	Adverse event (3), Protocol deviation (1), Lost of follow up (1), Other (1)	IE24, V24, NE, UED, DV
			67 (52/15	Experimental	THC/CBD	Max.	Spray	8	48.6	NR	50	Dizziness (12),	Adverse event (7), withdrawal	IE24, V24, NE, UED,

			)			129/120					(2 SAE)	Headache (4), Vomiting (4)	of consent (3), Other (1)	DV
Non-RCT	Brady et al. [18]	2004	21 (17/4)	Experimental	THC/CBD	Max. 120/120	Spray	8	48	11	21	Worsening of dry mouth	MS relapse, reaction at dosing visit, UTIs, cardiac problems, failure to comply (5)	IE24, DV, UED, NE, BEE, MCC
			15 (NR)	Experimental	THC	Max. 120	Spray	8	48	NR	15	Worsening of dry mouth	Failure to comply (1)	IE24, DV, UED, NE, BEE, MCC

BEE = bladder emptying efficiency (=volume voided x 100/(volume voided + post void residual); CBD = cannabidiol; DV = daytime voids; IE24 = incontinence episodes per 24 hours; MCC = maximum cystometric capacity; MS = multiple sclerosis; NE = nocturia episodes (%); NR = not reported; PT = pad test; RCT = Randomized controlled trial; SAE = serious adverse event; THC = delta-9-tetrahydrocannabinol; UED = urgency episodes per day; UTI = urinary tract infection; V24 = voids per 24 hours

Table 2. Treatment outcomes of included studies

			Incontinence episodes per 24 hours				Nocturia episodes				Daytime voids				Voids per 24 hours				Urgency episodes per day			
Study	Inter-vention	Number of patients	BL	UT	Difference	P-value	BL	UT	Difference	P-value	BL	UT	Difference	P-value	BL	UT	Difference	P-value	BL	UT	Difference	P-value
Freeman et al. [17]	Con	81	1.4	0.568	(-18%)	-2.76**			NR				NR				NR				NR	
	Exp	86	2.5	1.864	(-33%)	-5.63**			NR				NR				NR				NR	
	Exp	88	1.5	0.914	(-38%)	-6.55**			NR				NR				NR				NR	
Kavia et al. [16]	Con	64	2.1	1.12	-0.98	0.569	1.5	1.26	-0.24	0.01	NR	NR	-0.66	0.044	NR	NR	-0.9	0.007	NR	NR	-1.12	0.07
	Exp	60	1.8	0.72	-1.08		1.6	1.08	-0.52		NR	NR	-1.23		NR	NR	-1.75		NR	NR	-1.88	
Brady et al. [18]	Exp	13	2.14	0.9	-1.24*	NR	1.79	0.8	-0.88	NR	10.2	7.38	-2.82	NR			NR		16†	6†	-10†	NR
	Exp	13	0.9	0.267	-0.63*	NR	0.9	0.9	0	NR	7.38	6.43	-0.95	NR			NR		6†	4†	-2†	NR

All reported values are means, except for * = median; ** = z value; † = percentage of patients reporting at least 1 urgency episode per day; BL = baseline; Con = control intervention; Exp = experimental intervention; NR = not reported; UT = under treatment; P-value = p-value of group comparison at same time point